To: Ron DeHaven, Deputy Administrator, Veterinary Services, APHIS

From: Joshua Cohen and George Gray, Harvard Center for Risk Analysis

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Re: Comments on USDA bovine spongiform encephalopathy (BSE) surveillance plan

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At the request of USDA, the Harvard Center for Risk Analysis has reviewed the Department's draft surveillance plan (USDA, 2004) designed to better estimate the prevalence of BSE in the U.S. cattle population. The draft plan addresses a number of issues, including the number of animals to test for BSE, which types of animals to test, sample collection logistics, costs, and communications. Our comments provide advice on how to best use the information gathered by surveillance for the purpose of estimating the overall prevalence of BSE in the U.S. cattle population. While we do not have the technical expertise to address other issues relevant to the plan, USDA's treatment of these issues seems appropriate to us.

In summary, we agree with USDA's focus on testing high risk cattle. If there are additional BSE-infected animals in the U.S., the likely high false negative rate for laboratory detection of BSE in normal adults and juveniles (animals that do not yet show signs of disease) would make a focus on these populations inefficient. The main interpretation challenge for USDA is the extrapolation of test results from the high risk cattle population to normal adult and juvenile cattle. Doing so requires the development of explicit assumptions about how the BSE prevalence rates in these sub-populations are related. We propose an approach and develop some initial estimates for these assumptions.

Before proceeding, we note that estimating the prevalence of BSE requires further consideration of USDA's goals. On the one hand, USDA could choose to estimate the prevalence detectable BSE in the U.S. cattle population. Here, we refer to the fact that current tests can only detect BSE near the end of the disease incubation period. Such an approach would not account for animals that are infected but have disease that is not detectable. These estimates have the advantage of being comparable to estimates reported by other countries, which also report the prevalence of detectable BSE. The detectable animals also pose a much greater risk than non-detectable animals because they have a much greater amount of infectivity. We describe how both prevalence rates can be estimated.

As we understand it, USDA's plan proposes the laboratory testing of as many high risk cattle as is practical (amounting to 268,444, based on statistical and other considerations), and 10,000 adult cattle that are clinically normal. The high risk population represents 445,886 cattle, including 251,532 adult cattle that die on the farm, 194,225 satisfying FSIS condemnation criteria (non-ambulatory cattle, cattle with CNS signs and/or rabies negative, cattle with other signs potentially associated with BSE, and dead cattle), and 129 foreign disease investigation animals.

USDA explains that its sampling of the high risk population is sufficient to detect a prevalence rate of one case in 10 million, which when applied to the entire population of adult cattle (45 million), corresponds to a total prevalence of approximately five animals. USDA does not explicitly quantify the prevalence rate that could be detected by its sampling of 10,000 normal adult cattle, but using their calculations (which are based on formulas described by Cannon and Roe (1982)), we calculate that they can detect a prevalence rate of 3×10^{-4} with 95% certainty.

We note that USDA's derivation of a sensitivity level for their surveillance plan (one in 10 million animals with 99% certainty) assumes that all the infected animals in the U.S. belong to the high risk population group. In particular, USDA correctly calculated that the proposed plan would detect the presence of BSE with 99% certainty if as many as five high risk cattle had BSE. Dividing five into the adult cattle population size of 45 million yields approximately one in 10 million. However, because there may be BSE-infected animals in the normal adult and normal juvenile populations, a more rigorous set of assumptions must be developed to estimate a prevalence for the entire population.

For the purpose of quantifying the relationship between prevalence among high risk cattle and prevalence in the normal adult and normal juvenile sub-populations, we first define the population of interest to be those cattle that die or are slaughtered each year. For the purpose of quantifying the prevalence <u>rate</u> for the entire cattle population (including those that are alive), this definition leads to an upper bound because cattle that are slaughtered or that die are at higher risk for BSE than cattle that continue to live because the former have lived longer and have had more opportunities to be exposed to the BSE agent. On the other hand, for the purpose of quantifying the total prevalence (number of BSE positive cattle) for the entire cattle population, our definition leads to a lower bound. However, because only animals that die or are slaughtered can cause the spread of the disease to other cattle or exposure of humans to BSE-contaminated tissues, it is the

BSE prevalence among cattle that die or are slaughtered that is most relevant from a risk management perspective.

The remainder of this memo reviews alternative approaches for estimating BSE prevalence. The first approach depends on direct measurement of BSE in the component cattle sub-populations. We explain that high false positive rates in the normal sub-populations render this approach inefficient. The second approach focuses surveillance efforts on the high risk population and uses the estimated prevalence in this group to estimate the prevalence in the other groups.

1 Direct measurement of BSE prevalence in cattle sub-populations

This approach estimates BSE prevalence for the entire cattle population by adding the prevalence values for each group. The total number of BSE cases (n_{Total}) is $n_{HR} + n_A + n_J$, where the *HR* subscript refers to the population of "high risk" animals, the *A* subscript refers to normal adult animals, and the *J* subscript refers to normal juvenile animals. Table 1 defines these sub-populations based on the animal's age and whether it displays clinical signs of disease.

Table 1
Cattle Sub-Population Definitions

	Age < 24 months	**Age 24 to 29 months[(a)]**	**Age ≥ 30 months**
No clinical signs	Normal Juvenile	Normal Juvenile	Normal Adult
Clinical Signs	Normal Juvenile	High Risk	High Risk

Notes:

(a) We consider adults to include cattle at least 30 months of age. However, consistent with the definition of its targeted cattle population (USDA, 2004, p. 2), we assume animals with clinical signs that are at least 24 months of age are in the high risk sub-population.

Estimates for each of these components ($\hat{n}_i$) can be calculated as the product of the sample prevalence rate ($\hat{r}_i$), the number of animals in each population (N_i), and an adjustment for the false negative test detection rate ($\frac{1}{1-FN_i}$). Hence, the total number of BSE cases can be estimated as

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$$\hat{n}_{Total} = \sum_i \hat{r}_i \times N_i \times \frac{1}{1 - FN_i}. \qquad \text{Eq 1}$$

If we optimistically assume the false negative rate is zero, this approach and USDA's proposed surveillance plan would be capable of detecting with 95% certainty a prevalence rate of 2.8×10^{-4} among the 6.2 million normal adult and high risk cattle that die each year (*i.e.*, 1,740 BSE cases). However, this interpretation of the data provides no insight regarding the prevalence rate among normal juveniles (see Table 2).

Table 2
95% Upper Confidence Limit on BSE Prevalence if no Animals Test Positive: Estimates Based on Testing Only

Population	Number of Positive Detects	95% Upper Confidence Limit on r[(a)]	Number of Animals Slaughtered per Year	Assumed BSE False Negative Rate	95% Upper Confidence Limit on n
HR	0 of 268,444	7.3×10^{-6}	446,000	0	3
A	0 of 10,000	3.0×10^{-4}	5,800,000	0	1,736
J	0 of 0	-	30,000,000	-	n_J
Total					**1,739 +** $\boldsymbol{n_J}$

Notes:
(a) Estimated using Cannon and Roe (1982).

The sensitivity of this approach could in theory be substantially increased by testing the same proportion of animals in each sub-population. For example, testing approximately 4.4% of the high risk animals and 4.4% of the normal adults, *i.e.*, 20,000 high risk animals and 258,000 normal adults, would be capable of detecting a BSE prevalence of around 2×10^{-5} (132 positive animals among the 6.2 million normal adult and high risk cattle) with 95% certainty. However, this result depends on the assumption that the false negative rate is zero. It also continues to ignore the normal juvenile sub-population.

While the assumption of a zero false negative rate may be reasonable for full blown cases that would presumably belong to the high risk sub-population, this assumption is likely to be very optimistic for other cattle. After an animal is infected with BSE, definitive post mortem tests for the presence of the agent yield false negative results until not long before clinical signs develop. Although it is not known precisely when these tests become effective, a reasonable estimate is three months prior to the development of clinical signs (personal communication, Lisa Ferguson, USDA APHIS, Veterinary Services, March 1, 2004).

We have estimated the false negative rates for normal adult and normal juvenile animals using a modified version of Harvard's BSE simulation model. This modified version of the model reports the characteristics of each BSE-positive animal that dies during the simulation. Characteristics reported include the animal's type (dairy, beef, beef reproductive), gender, age (months), months since the animal was infected with BSE, fraction of the incubation period elapsed at time of death, and death location (farm or slaughter facility). We assume that animals with BSE test negative if less than 90% of their incubation period has elapsed. We simulated the spread of BSE for 20 years following the introduction of contaminated feed (250 ID_{50}s) into the U.S.[1] Our results indicate a false negative rate of 92% for normal adult cattle. For normal juvenile cattle, the false negative rate is 99.99%. Accounting for these false negative rates and the potential for BSE among normal juvenile animals suggests that the evaluating the surveillance data as described here is a relatively insensitive approach for detecting the presence of BSE in the U.S. cattle population.

Taking into account the false negative rates estimated in the previous paragraph (and continuing to ignore the normal juveniles for the moment) decreases the sensitivity of the "optimal" surveillance plan described earlier (20,000 high risk animals and 258,000 normal adults) so that only a BSE prevalence rate of 1.4×10^{-4} or greater can be detected.

2 Extrapolation of the BSE prevalence rate from the high risk sub-population to the normal sub-populations

The modeling approach described in this section uses empirical data or the Harvard BSE simulation to better characterize the relationship between BSE prevalence rates in different groups. In particular, we propose 1) estimating the number of BSE-positive animals in the high risk category using surveillance, and then 2) estimating the number of BSE-positive normal adults by scaling $\hat{n}_{HR}$ by an estimate of the ratio of n_A to n_{HR} (designated $Q_{A:HR}$). Similarly, $\hat{n}_J$ is estimated as $\hat{n}_{HR} \times Q_{J:HR}$. Hence, the total number of BSE-positive animals is estimated as

$$\hat{n}_{Total} = \hat{r}_{HR} \times N_{HR} \times \frac{1}{1 - FN_{HR}} \left(1 + Q_{A:HR} + Q_{J:HR}\right). \qquad \text{Eq 2}$$

[1] We simulated the introduction of contaminated feed, rather than the introduction of infected animals, because we did not want our results to be influenced by the characteristics of the animals introduced.

We present two ways to estimate the values of $Q_{A:HR}$ and $Q_{J:HR}$. First, we can estimate these ratios using similar empirical values measured in other countries. In Switzerland, the BSE prevalence rate among fallen stock (FS) and emergency slaughter (ES) animals aggregated over the years 1999 and 2000 was approximately eight times greater than the BSE prevalence rate among routine slaughter animals. Recall that USDA's proposal to test approximately 268,000 high risk animals would be sufficiently powerful to establish that the prevalence rate is no more than 7.3×10^{-6} with 95% certainty. Assuming a zero false negative rate and applying the prevalence rate ratio of eight from the Swiss data, this result would imply a BSE prevalence rate of 9.1×10^{-7} among normal adult cattle ($7.3 \times 10^{-6} \div 8$). This rate corresponds to a total prevalence among normal adult cattle of approximately 5 BSE cases (5.8 million $\times$ 9.1×10^{-7}). The Swiss data do not provide any information on the BSE prevalence rate among juvenile cattle. Nor do they take into account the potential for a higher false negative rate among normal adult cattle than among high risk cattle. Finally, as noted earlier, differences in agricultural practices across countries make extrapolation of results from Switzerland to the U.S. uncertain.

An alternative approach for estimating $Q_{A:HR}$ and $Q_{J:HR}$ uses the modified version of Harvard's BSE simulation model described earlier in this memo. We again consider the characteristics of cattle infected with BSE at the time of their death following the introduction of 250 ID_{50}s into cattle feed. Table 3 summarizes the distribution of values for $Q_{A:HR}$ and $Q_{J:HR}$ based on 1,000 simulation runs. We provide two sets of distributions. The first set of distributions pertains to the total BSE prevalence rate – *i.e.*, including all animals infected with BSE even if laboratory testing would be incapable of detecting the presence of the disease. The second set of distributions pertains to the prevalence of <u>detectable</u> BSE only. It is the second set of distributions that is relevant for the purpose of comparing U.S. prevalence to other countries because other countries estimate only the rate of detectable BSE in their cattle populations.

Table 3
Summary Statistics for the BSE Prevalence Ratios

Fractile	Total BSE Prevalence $Q_{A:HR}$	Total BSE Prevalence $Q_{J:HR}$	Prevalence Among Normal Adults and Juveniles of Detectable BSE Only $Q_{A:HR}$ (a)	Prevalence Among Normal Adults and Juveniles of Detectable BSE Only $Q_{J:HR}$ (b)
5th	0.42	1.55	0.034	1.5×10^{-4}
10th	0.50	1.82	0.040	1.8×10^{-4}
25th	0.73	2.29	0.058	2.3×10^{-4}
50th	1.00	3.00	0.080	3.0×10^{-4}
75th	1.50	4.20	0.12	4.2×10^{-4}
90th	2.25	6.25	0.18	6.3×10^{-4}
95th	3.00	8.33	0.24	8.3×10^{-4}

Notes:

(a) Assumes a false negative rate of 92%.
(b) Assumes a false negative rate of 99.99%.

Estimating the total BSE prevalence

Using the median values from columns 2 and 3 of Table 3 in Equation 2, along with the assumption that the false negative rate is zero for BSE-positive cases in the high risk group, testing 268,000 animals from the high risk group would be capable of detecting a BSE prevalence ($\hat{n}_{Total}$) of around 16 with 95% certainty (3.25 × (1 + 1.0 + 3.0)). Using the upper 95th percentile values for these ratios yields an upper bound for $\hat{n}_{Total}$ of around 40 (3.25 × (1 + 3.0 + 8.3)). Because the total number of animals slaughtered in the U.S. each year is approximately 35 million, 40 animals corresponds to a prevalence rate one per one million cattle that die or are slaughtered. More refined bounds could be calculating by developing estimates for $Q_{A:HR}$ and $Q_{J:HR}$ using more realistic scenarios for the introduction of BSE into the U.S. and by establishing a more relevant time horizon for the simulation.

Estimating the prevalence of detectable BSE

Using the median ratios in columns 4 and 5 of Table 3 in Equation 2, testing 268,000 animals from the high risk group can detect a prevalence of approximately 3 with 95% certainty, a level that corresponds to a prevalence rate of approximately 1 per 10 million cattle that die or are slaughtered. Even the upper bound estimates from columns 4 and 5 yield virtually the same result.

While the ratios in columns 4 and 5 of Table 3 are most appropriate for comparing the prevalence of BSE in the U.S. to the BSE prevalence in other countries, it is reasonable to ask what level of risk (to humans or other cattle) the non-detectable cases might pose. Using the simulation described earlier, we estimate that the average infectivity loads in normal juveniles and normal adults that have non-detectable BSE are approximately 120 and 130 cattle oral ID_{50}s, respectively. Because they are slaughtered at a young age, there are virtually no juveniles that reach the detectable stage of the disease. However, among normal adults that reach the detectable stage, the infectivity load is more than 20 times greater (average of 2,800 cattle oral ID_{50}s). Of course, the average infectivity load in animals that reach full clinical status is higher still, at 10,000 cattle oral ID_{50}s.

References

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